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(57) Abstract			
<p>The invention relates to the use of 2,3-benzodiazepine derivatives for the preparation of pharmaceutical compositions useful for the treatment or prevention of diseases connected with the endogenous opioid system, particularly disturbances of the hedonic state. Particularly preferable 2,3-benzodiazepine derivatives for use according to the present invention are the following compounds: 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (tofisopam), 1-(3-chlorophenyl)-4-methyl-7,8-dimethoxy-5H-2,3-benzodiazepine (girisopam), or 1-(4-aminophenyl)-4-methyl-7,8-dimethoxy-5H-2,3-benzodiazepine (nerisopam).</p>			

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USE OF 2, 3-BENZODIAZEPINE DERIVATES FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS TO TREAT DISEASES CONNECTED WITH THE ENDOGENOUS OPIOID SYSTEM

Technical field of the invention

This invention relates to the use of 2,3-benzodiazepine derivatives for the preparation of pharmaceutical compositions useful for the treatment or prevention of diseases connected with disturbances of the opioid system.

Background of the invention

Hedonia (the overstated demand of pleasure), as well as ahedonia (inability to feel pleasure) are known characteristic symptoms of different mental diseases. These symptoms are mentioned in the Diagnostic and Statistical Manual of Mental Disorders, IV. ed. (American Psychiatric Association, Washington D.C., USA, 1994) among diagnostic criteria for schizophrenia and depression. In the development of drug addiction and alcoholism the increased desire of pleasure is considered to play an important role by initiating the progress of disease state [Drug addiction and alcoholism and opioid signals, Koob, G.F. Ann. N.Y. Acad. Sci.: 654:1171-191 (1992)]. Under psychological circumstances the state of pleasure is primarily the consequence of specific actions of the endogenous opioid peptides [(Berridge, K.C.: Neurosci. Biobehav. Rev. 20:1-25 (1996)]. There is a double specificity of action of the endogenous opioid peptides: on the one hand the opioid peptide is released and acts only in areas of the brain performed to evoke the state of pleasure,

on the other hand the appropriate receptor of the opioid peptides is activated on the effect of stimuli evoking pleasure. The main opioid receptor types, namely μ , κ and δ do not play equal roles in producing the feeling of pleasure.

Summary of the invention

The present invention is based on the recognition that the effect of 2,3-benzodiazepine derivatives on the behaviour of experimental animals is inhibited in states of opioid tolerance induced by morphine. This means that the compounds are acting via the opioid signal transduction system. Consequently, the 2,3-benzodiazepines may be employed in the therapy or prevention of disease states in which the endogenous opioid system is playing a role. Disturbances of the hedonic state (increased or depressed ability of feeling pleasure) are the most characteristic examples of these symptoms of diseases.

The objects of the present invention are as follows:

- to provide pharmaceutical compositions containing as active ingredient a 2,3-benzodiazepine derivative useful for the treatment or prevention of diseases connected with the opioid system, particularly disturbances of the hedonic state,
- to provide a process for the preparation of pharmaceutical compositions suitable for the treatment or prevention of diseases connected with the disturbances of the endogenous opioid neural system, particularly disturbances of the hedonic behaviour,

- to provide a method of use of 2,3-benzodiazepine derivatives for the treatment or prevention of the above-mentioned diseases,
- to provide a process for the treatment or prevention of the above-mentioned diseases by applying 2,3-benzodiazepine derivatives.

Detailed description of the invention

According to the present invention the following 2,3-benzodiazepine derivatives are preferably used:

- 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (tofisopam),
- 1-(3-chlorophenyl)-4-methyl-7,8-dimethoxy-5H-2,3-benzodiazepine (girisopam), or
- 1-(4-aminophenyl)-4-methyl-7,8-dimethoxy-5H-2,3-benzodiazepine (nerisopam).

According to a preferred embodiment of the present invention the following 2,3-benzodiazepine derivative is used:

- 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (tofisopam).

The efficacy of 2,3-benzodiazepines in the treatment of hedonic disturbances was proved by the following experiments:

Experiments:

The experiments were carried out in Charles River Wistar rats. The animals were treated subcutaneously with saline or morphine for 4 consecutive days. Treatments were carried out twice a day between 8 and 9 o'clock a.m. and

between 17 and 18 o'clock p.m. The group treated with morphine received on the first day two times 5 mg/kg, on the second day two times 10 mg/kg, on the third day two times 15 mg/kg and on the fourth day two times 20 mg/kg of morphine. This treatment schedule decreases the analgesic potency of morphine to about one fifth 18 hours after the last treatment. The test compounds, that is the 2,3-benzodiazepine derivatives were administered on the fifth day. On the fifth day of the experiment, 15-20 hours after the last treatment, open field tests were carried out as specified in the literature [(Van Ree, J.M., G. Wolternik: "Motility and grooming as measures of anxiolysis with homophtalazines", Eur. J. Pharmacol. 72:107-111 (1981)]. The motility (the number of crossing one of the lines among the 16 squares on the surface of the open field) and the number and length of grooming periods were measured during an observation period of 10 minutes.

The obtained results show that the tested 2,3-benzodiazepines decreased the motility (Tables 1-3 and Figure 1) of the test animals. In parallel with the decrease of motility the frequency and length of the grooming period increased, too. These effects indicate the anxiolytic property of the test compounds [(K. Horváth, F. András, P. Botka, T. Hámori: Acta Physiol. Hung. 79., 153-161 (1992)]. In the state of morphine tolerance the above-described effects of the compounds disappeared or basically decreased.

Table 1

The effect of topisopam in open field test in rats

S.E.: standard error of the mean, n: number of measurements

	Motility/10 min			Grooming			Grooming time		
	number of crossings			number/10 min			(sec)		
Saline-treated	Mean	±S.E.	n	Mean	±S.E.	n	Mean	±S.E.	n
Control	182.8	19.5	9	2.87	0.54	9	27.1	5.83	9
tofisopam 20 mg/kg	143.4	14.0	9	4.66	0.97	9	42.0	10.1	9
tofisopam 40 mg/kg	110.5	11.0	9	6.88	1.29	9	64.9	14.2	9
tofisopam 80 mg/kg	100.3	17.4	9	6.11	1.64	9	97.0	24.2	9
Morphine tolerant									
Control	106.6	12.0	10	5.0	1.22	10	80.9	26.4	10
tofisopam 20 mg/kg	83.9	6.64	10	6.6	1.35	10	72.8	9.34	10
tofisopam 40 mg/kg	69.1	11.5	10	4.2	1.21	10	62.1	18.7	10
tofisopam 80 mg/kg	60.8	10.2	10	5.33	1.23	10	86.3	21.2	10

Table 2

The effect of nerisopam in open field test in rats

S.E.: standard error of the mean, n: number of measurements

	Motility/10 min			Grooming			Grooming time		
	number of crossings			number/10 min			(sec)		
Saline-treated	Mean	±S.E.	n	Mean	±S.E.	n	Mean	±S.E.	n
Control	158.1	10.2	19	4.00	0.78	19	10.5	3.00	13
nerisopam 0.3 mg/kg	161.0	28.8	5	5.60	1.28	5			
nerisopam 0.6 mg/kg	121.9	22.1	10	6.00	1.28	10	22.0	6.85	5
nerisopam 1.2 mg/kg	92.5	14.9	10	3.00	0.59	10	22.8	8.30	5
Morphine tolerant									
Control	109.9	10.8	10	4.60	1.03	10	80.6	36.8	10
nerisopam 0.3 mg/kg	129.3	34.0	5	3.33	1.52	5			
nerisopam 0.6 mg/kg	92.8	9.52	10	5.80	1.35	10	61.8	20.9	10
nerisopam 1.2 mg/kg	115.8	6.06	10	3.72	0.63	10	25.6	12.0	10

Table 3

The effect of girisopam in open field test in rats

S.E.: standard error of the mean, n: number of measurements

	Motility/10 min number of crossings			Grooming number/10 min			Grooming time (sec)		
Saline- treated	Mean	±S.E.	n	Mean	±S.E.	n	Mean	±S.E.	n
Control	148.4	8.18	27	3.62	0.70	27	13.6	2.67	21
girisopam 3 mg/kg	61.70	19.6	4	8.00	0.59	4	51.6	17.8	4
girisopam 6 mg/kg	83.0	17.1	8	3.87	0.81	8	53.8	14.0	8
girisopam 12 mg/kg	75.5	11.1	4	8.75	2.32	4	95.1	17.5	4
Morphine tolerant									
Control	122.9	11.9	10	2.90	0.60	10	49.6	20.5	10
girisopam 3 mg/kg	96.4	17.0	5	4.60	1.07	5	80.4	34.8	5
girisopam 6 mg/kg	124.2	8.89	10	5.50	1.88	10	48.8	18.9	10
girisopam 12 mg/kg	100.4	13.5	5	4.80	0.96	5	47.6	9.20	5

Further results are shown in Figure 1.

Explanation

Figure 1 shows the effect of tofisopam, nerisopam and girsopam on the motility and grooming behaviour of rats in open field test after treatment with saline or morpholine. The results of Tables 1-3 are presented as percentages of the control values. The vertical bars indicate the standard errors of the mean, *P 0.05, **P 0.01 (analysis of variance followed by Duncan test).

The above results show that the state of morpholine tolerance inhibits the anxiolytic effect of 2,3-benzodiazepines. The surprising results prove that the said compounds exert their action via the opioid receptoral mechanism. The inhibition of an effect by morphine tolerance (in a state when the opioid neuronal system is relatively intensive towards compounds acting on specific receptors) is an accepted evidence to prove that an action is mediated by opioids. In this latter case the effect of a given compound is inhibited by opioid tolerance [(Martin, W.R., C.G. Eades, J.A. Thompson, R.E. Huppler, P.E. Gilbert: *J. Pharmacol. Exptl. Ther.*, 197:517-532 (1976)].

Consequently, the 2,3-benzodiazepines induce their psychopharmacological effects (anxiolysis) due to an action on the endogenous opioid system evoking good feeling, pleasure. This effect envisages that the 2,3-benzodiazepine derivatives may be employed to treat or prevent hedonic disturbances. These disturbances are present in cases of schizophrenia, depression, alcoholism or drug dependence.

In cases of schizophrenics with anhedonia the 2,3-benzodiazepine derivatives increasing the feeling of pleasure decrease the desire for drug or alcohol. Similarly, depression induced by stress or loss of weight of animals induced by stress may be counteracted by 2,3-benzodiazepines.

The doses of the 2,3-benzodiazepine derivatives are shown in the following Table:

Active ingredient	Single dose (mg)	Maximum oral dose (mg)
tofisopam	25-100	600
girisopam	10-100	500
nerisopam	1-100	150

The pharmaceutical compositions of the present invention useful for the treatment or prevention of diseases connected with the opioid system can be prepared by methods known per se by admixing the active ingredient with suitable inert solid or liquid carriers and bringing the mixture to galenic form.

The pharmaceutical compositions of the present invention can be presented preferably in the form of orally administerable preparations (such as tablets, pills, coated pills, soft or hard gelatin capsules, solutions or suspensions etc.), or as compositions for parenteral (e.g. injection solutions), rectal (e.g. suppositories) or nasal (e.g. aerosols) administration. The pharmaceutical compositions may release the active ingredient at once, in which case the

duration of the effect depends only on the duration of effect of the applied ingredients. When applying special pharmaceutical compositions, however, the release of the active ingredient may be prolonged, and in this case the duration of the therapeutic effect is influenced by the form of the pharmaceutical composition as well (sustained-release or controlled-release preparations).

The pharmaceutical compositions can be prepared by methods generally applied in the pharmaceutical industry.

In the course of further processing the product to tablets different kinds of lactose (monohydrate, anhydrate, spray-dried substances, etc.), inorganic salts (secondary calcium phosphate, calcium sulfate, calcium carbonate, etc.) may be applied as fillers. As binding agents gelatin, polyvinyl pyrrolidone, different cellulose ethers (hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, etc.), hydrolyzed starches, various vegetal gums (gum arabic, guar gum) may be applied in solutions formed with water, C₁₋₄ aliphatic alcohols or the mixtures thereof. As disintegrant various kinds of starches (potato, corn, wheat, etc.) as well as super-disintegrants (carboxymethyl cellulose [the commercial product known as Ac-di-sol], carboxymethyl starch Na [commercial products known as Primojel, Ultraamilopectin, Explo-Tab], polyvinyl polypyrrolidone [the product of trade name Poliplasdone], etc.) may be used. As lubricant or fluidity improving auxiliary material alkali metal stearates (such as magnesium or

calcium stearate), fatty acids (stearic acid), various glycerides (e.g. products of the trade name Precirol, Cutina H), paraffin oil or silicon oils, silicon oil emulsions, talc or silica may be used.

The preparation of the active ingredients and auxiliaries for the tabletting procedure may be carried out by dry or damp granulation, or - when applying directly compressable auxiliaries, such as microcrystalline cellulose, spray-homogenized lactose, Tablettose, Cellactose, etc. - by a simple spray-homogenization. If desired, the granules or the spray-homogenized ingredients, instead of being tabletted, may also be filled into hard gelatin capsules. In this way hard gelatin capsule formulations can be prepared.

For the preparation of controlled release (retard) solid pharmaceutical dosage forms all the technologies known from the literature may be applied. So various matrix preparations may be prepared, wherein hydrophilic polymers (such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, polyacrylic acid derivatives, polysaccharoses, guar gum, xanthan gum, etc.) and mixtures thereof or hydrophobic polymers (such as ethyl cellulose, metacrylic acid ester copolymers, polyvinyl acetate, polyvinyl butyral, etc. and mixtures thereof) may be applied as retarding matrix substance. The matrix having a function of retarding the release of the active ingredient may, however, be produced by the application of mixtures of hydrophilic and hydrophobic polymers, as well as by the

application of mixtures of polymer substances and fat-like substances. The matrix preparations may also be prepared in the form of multi-layer tablets by incorporating the ingredients in different layers each. In this way the release profile of the ingredients can more readily be adjusted to their individual pharmacokinetic properties.

The controlled-release preparations containing the active ingredients according to the present invention may also be produced in the form of coated pellets. The preparation of pellets can be carried out either from the individual active ingredients or from mixtures thereof. The pellets may be prepared by extrusion spherization, rotogravitation or placebo layering methods. The pellets may be coated in rotating or fluidization apparatus. As coating agent solutions of water-insoluble polymer substances in organic solvents (usually in C₁₋₃ aliphatic alcohols and/or C₁₋₂ chlorinated carbohydrates containing two or more chlorine atoms, acetone and/or ethyl acetate or the mixtures thereof), or aqueous dispersions of same may be applied.

If desired, the active ingredients of the present invention may also be finished in the form of osmotic or diffusion-osmotic preparations. In this case tablets containing hydrophilic polymers (e.g. hydroxypropyl methyl cellulose) are prepared from the active ingredients, these tablets are then coated by methods known from the literature with a semipermeable (such as cellulose acetate) or permeable (such as aminomethacrylate copolymer) film layer, and a

passageway is bored into the layer through which the active ingredient can be osmotically pressed into the aqueous medium.

By suitable preparation of the sustained release compositions the setting free velocity of the active ingredient may be preferably adjusted to the rate that at least 80 % of the active ingredient should be released in vitro within 2 to 24 hours (measured as specified in the pharmacopoeias).

When preparing pharmaceutical preparations in liquid form, either the pH value of the preparations is adjusted so that it does not exceed 5 because of the poor solubility in aqueous medium of the 2,3-benzodiazepine derivatives at pH values higher than 5, or substances improving the solubility (cosolvents) have to be applied. Such cosolvents may be e.g. the following substances: ethyl alcohol, propylene glycol, polyethylene glycol, sorbite, cyclodextrines, surface active agents, polyethylene glycol/polypropylene glycol copolymers, etc.

When injectable compositions are produced, usually only preparations containing organic cosolvents may be formed because of the above considerations. In these preparations, in addition to the above-mentioned cosolvents further substances (such as benzyl alcohol, dimethyl acetamide, methylpyrrolidone, etc.) may also be applied. If desired, the injections may be produced in the form of emulsion preparations as well. In this case the ingredients, in the form of bases, are dissolved in liquid, fat-like auxiliary

substances (such as soya oil) and the emulsification of the oily solution in aqueous medium is carried out by the application of surface active agents (e.g. lecithins).

Suppository preparations may be prepared by methods known from the literature. The ingredients are dissolved or suspended in the melted suppository matrix, then the liquid mixture is poured into suppository forms or into small, suppository-shaped polymer blisters pre-fabricated from a polymer film and solidified by cooling. As binding material either natural (e.g. cocoa butter) or synthetic fat-like substances (e.g. commercial products of the trade name Witepsol) may be applied.

When using aerosol-type preparations, the active ingredient gets to the respiratory system in the form of sprayed drops or powder/air suspension. In case of the active ingredients according to the invention primarily formulations suitable for nasal administration may be applied. When preparing such formulations the solution or suspension of the active ingredients is filled into holders supplied with a proportioning valve either with or without the application of a power-gas. When no power-gas is used, a nozzle supplemented with a proportioning pump is to be applied.

The invention is further illustrated by the following Examples of non-limiting character:

Example 1Preparation of tablets

5 parts by weight of tofisopam and 9 parts by weight of lactose are admixed with 3 parts by weight of microcrystalline cellulose. The powder mixture is granulated in a rotary fluid granulator with the solution of 0.5 parts by weight of polyvinyl pyrrolidone in 4 parts by weight of ion-exchanged water. The granules are then dried, 1.3 parts by weight of carboxymethyl cellulose and 0.2 parts by weight of magnesium stearate are added to it and the mixture is passed through a 1.0 mm mesh sieve. The thus obtained granules are made up into tablets on a rotary tabletting machine by using a tabletting tool 8 mm in diameter. Thus tablets containing 50 mg of active ingredient are prepared (average weight: 200 mg).

Example 2Preparation of hard gelatin capsules

The sieved granules prepared according to Example 1 are filled into hard gelatine capsules of size No. 2.

Example 3Preparation of sustained release tablets

5 parts by weight of girsopam are mixed with 8 parts by weight of hydroxypropyl methyl cellulose (commercial name: Metocel K 4 M, made by Colorcon Ltd.) and 10 parts by weight of lactose. The powder mixture is granulated in a spiral air stream granulator with the solution of 0.4 parts by weight of polyvinyl pyrrolidone in isopropanol. The granules are dried and 0.3 parts by weight of talc and 0.3 parts by

weight of magnesium stearate are added to it. The granules are then passed through a 1.0 mm mesh sieve, pressed into tablets with the aid of a rotary tabletting machine by using a 10 mm diameter lenticular pressing tool. Thus tablets containing 50 mg of active ingredient are prepared (average weight: 300 mg).

Example 4

Preparation of suppositories

5 parts by weight of tofisopam are dispersed in 55 parts by weight of suppository matrix (Witepsol S 58, commercial trade name) at a temperature of 50°C. The suspension, while still liquid, is filled into suppository forms, the suppositories are solidified by cooling to a temperature of 25°C and removed from the forms. Thus suppositories average weight of the thus obtained suppositories containing 50 mg of active ingredient are prepared (average weight: 6 g).

What we claim is:

1. Use of 2,3-benzodiazepine derivatives for the preparation of pharmaceutical compositions useful for the treatment or prevention of diseases connected with the endogenous opioid system, particularly disturbances of the hedonic state.
2. A use as claimed in claim 1, which comprises applying as 2,3-benzodiazepine
 - 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (tofisopam),
 - 1-(3-chlorophenyl)-4-methyl-7,8-dimethoxy-5H-2,3-benzodiazepine (girisopam), or
 - 1-(4-aminophenyl)-4-methyl-7,8-dimethoxy-5H-2,3-benzodiazepine (nerisopam).
3. A use as claimed in claim 2, which comprises applying as 2,3-benzodiazepine 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (tofisopam).
4. Pharmaceutical compositions useful for the treatment or prevention of diseases connected with the endogenous opioid system, particularly disturbances of the hedonic state, comprising as active ingredient a 2,3-benzodiazepine derivative together with inert, solid or liquid pharmaceutical carriers and/or auxiliaries.

5. Pharmaceutical compositions as claimed in claim 4 comprising as active ingredient a compound according to claim 2.

6. A process for the preparation of pharmaceutical compositions comprising as active ingredient a 2,3-benzodiazepine derivative, which comprises admixing the active ingredient with carriers and/or auxiliaries generally used in the pharmaceutical industry and converting the mixture into pharmaceutical compositions suitable for the treatment or prevention of diseases connected with the endogenous opioid system, particularly disturbances of the hedonic state.

7. A process as claimed in claim 6, which comprises using as active ingredient

1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (tofisopam),

1-(3-chlorophenyl)-4-methyl-7,8-dimethoxy-5H-2,3-benzodiazepine (girisopam), or

1-(4-aminophenyl)-4-methyl-7,8-dimethoxy-5H-2,3-benzodiazepine (nerisopam).

8. A process as claimed in claim 7, which comprises using as active ingredient 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (tofisopam).

9. A process as claimed in any of claims 6 to 8, which comprises preparing a pharmaceutical composition suitable for oral, rectal or parenteral administration.

10. A process as claimed in claim 9, wherein the said pharmaceutical composition is in the form of tablets, capsules, dragées, solutions, suspensions, suppositories or injections.

11. A process as claimed in any of claims 9 or 10, which comprises preparing pharmaceutical compositions in the form of tablets, capsules, dragées, solutions, suspensions, suppositories or injections containing 5 to 100 mg of active ingredient.

12. A method for the treatment or prevention of diseases connected with the endogenous opioid system, particularly disturbances of the hedonic state, which comprises administering to a patient in need of such treatment a therapeutically effective amount of a 2,3-benzodiazepine derivative.

13. A method as claimed in claim 12, which comprises administering a 2,3-benzodiazepine derivative specified in claim 2.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/HU 98/00069

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/55

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 322 346 A (KOROSI JENO ET AL) 30 March 1982 see column 4, line 11 - line 12 see column 4; table 1 see column 10; example 39 ---	1,2,4-7, 9-13
X	US 3 736 315 A (KOROSI J ET AL) 29 May 1973 see column 2, line 28 - line 34 ---	4-9
X	GB 2 248 838 A (EGYT GYOGYSZERVEGYESZETI GYAR) 22 April 1992 see page 2, line 3 see page 7, line 32 - page 8, line 16 ---	1,4,6, 9-12

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- "O" document referring to an oral disclosure, use, exhibition or other means
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 1998	02/11/1998
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Trifilieff-Riolo, S

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/HU 98/00069

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANDRASI ET AL: "neuropharmacology of a new psychotropic 2,3-benzodiazepine" ARZNEIMITTELFORSCHUNG, vol. 37, no. 10, 1987, pages 1119-1124, XP002081293 see abstract ---	1,2,4-7, 9-13
X	HORVATH ET AL: "a new psychoactive 5H-2,3-benzodiazepine with a unique spectrum of activity" ARZNEIMITTELFORSCHUNG, vol. 39, no. 8, 1989, pages 894-899, XP002081294 see page 898, right-hand column ---	1,2,4-7, 9-13
X	VARADY ET AL: "clinical evaluation of grandaxin used in the treatment of outpatients" THERAP HUNGAR, vol. 23, no. 4, 1975, pages 153-158, XP002081295 see page 154; table 1 see page 153, right-hand column ---	1-13
X	KARDOS: "alcohol dependence, withdrawal syndrome and "tapering off" therapy" ORV HETIL, vol. 120, no. 39, 1979, pages 2343-2349, XP002081296 see page 2348, column G, paragraph 3 ---	1-13
X	BOSZORMENYI: "clinical and therapeutical problems of mild mental depressions" THERAP HUNGAR, vol. 23, no. 4, 1975, pages 156-162, XP002081297 see page 151, left-hand column ---	1-13
X	BANKI: "comparative study with grandaxin and diazepam in alcohol withdrawal syndrome and gerontopsychiatric diseases" THERAP HUNGAR, vol. 31, no. 3, 1983, pages 120-125, XP002081298 see page 121, left-hand column ---	1-13
X	POIRIER: "indications des benzodiazepines dans la prise en charge des toxicomanes" ANN MED INTERNE, vol. 145, no. 3, 1994, pages 52-53, XP002081299 see page 52; table 1 ---	1-10,12, 13
	-/-	

INTERNATIONAL SEARCH REPORT

Int'l. Application No.
PCT/HU 98/00069

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOLCAN: "tofizepam in the therapy of anxious-depressive syndromes" AGRESSOLOGIE, vol. 22, 1981, pages 23-24, XP002081300 see page 23, right-hand column -----	1-13
X	NAKAGAWA: "treatment of psychosomatic disorders" ASIAN MED J, vol. 33, no. 5, 1990, pages 250-258, XP002081301 see page 254; table 3A -----	1-10,12, 13

INTERNATIONAL SEARCH REPORT

...nternational application No.

PCT/HU 98/00069

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 12 & 13
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.

2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking(Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No
PCT/HU 98/00069

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 4322346	A 30-03-1982	AT	373589 B	10-02-1984
		AT	647279 A	15-06-1983
		AU	532079 B	15-09-1983
		BE	879404 A	15-04-1980
		BG	60270 B	31-03-1994
		CA	1125749 A	15-06-1982
		CH	643835 A	29-06-1984
		CS	236456 B	15-05-1985
		DD	146596 A	18-02-1981
		DE	2940483 A	30-04-1980
		DK	440179 A,B,	20-04-1980
		FI	793209 A,B,	20-04-1980
		FR	2439189 A	16-05-1980
		GB	2034706 A,B	11-06-1980
		GR	74034 A	06-06-1984
		JP	1505220 C	13-07-1989
		JP	55092377 A	12-07-1980
		JP	63050354 B	07-10-1988
		NL	7907692 A,B,	22-04-1980
		SE	439919 B	08-07-1985
		SE	7908481 A	20-04-1980
		SU	1402258 A	07-06-1988
US 3736315	A 29-05-1973	AT	279617 B	10-03-1970
		AT	278797 B	10-02-1970
		BE	707730 A	16-04-1968
		CH	519507 A	29-02-1972
		DE	1670642 A	18-03-1971
		DK	125650 B	19-03-1973
		DK	118660 B	21-09-1970
		FR	6852 M	08-04-1969
		NL	6716753 A,B	10-06-1968
		SE	324154 B	25-05-1970
		US	RE30014 E	29-05-1979
GB 2248838	A 22-04-1992	AT	399506 B	26-05-1995
		AT	207191 A	15-10-1994
		AU	648111 B	14-04-1994
		AU	8592291 A	30-04-1992
		BE	1004995 A	16-03-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No
PCT/HU 98/00069

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2248838	A	CA 2053622 A	18-04-1992
		CH 682400 A	15-09-1993
		CN 1060838 A, B	06-05-1992
		CS 9103141 A	13-05-1992
		DE 4134402 A	14-05-1992
		DK 174891 A	18-04-1992
		ES 2036137 B	01-03-1994
		FI 914918 A	18-04-1992
		FR 2668148 A	24-04-1992
		GR 91100426 A, B	25-09-1992
		HU 9500268 A	28-09-1995
		IL 99637 A	18-06-1996
		IT 1256279 B	29-11-1995
		JP 4282374 A	07-10-1992
		NL 9101741 A	18-05-1992
		PL 167108 B	31-07-1995
		SE 506380 C	08-12-1997
		SE 9103022 A	18-04-1992
		RU 2058982 C	27-04-1996
		US 5204343 A	20-04-1993
		ZA 9108273 A	04-10-1994